REMARKS

Claim 103 is pending in the Application and stands rejected. Claims 1, 2, 5, 8-13, 16-19, 29-37, 40, 43-60 and 104-108 are cancelled herein without prejudice.

In light of these amendments and the following remarks, Applicants respectfully request reconsideration and allowance of claim 103.

Interview Summary

Applicants thank the Examiner for the courtesy of the telephonic interview of June 5, 2009. During the interview, the election of Group 2, claim 103, was discussed.

Rejections under 35 U.S.C. § 112

Enablement

The Examiner rejected claim 103 under 35 U.S.C. § 112, first paragraph, alleging that it lacks enablement. Specifically, the Examiner alleged that the specification does not enable one having ordinary skill in the art to make and use the claimed invention without undue experimentation. The Examiner also alleged that pre- and post-filing date art teach that the detection of sequence variants in the *PKHD1* gene is "highly unpredictable." (Office Action at page 5.)

Applicants respectfully disagree. The test for enablement is whether one skilled in the art at the time Applicants filed would have been able to make and use the claimed invention from the disclosures in the specification, coupled with the information known in the art without undue experimentation. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). The law recognizes that a considerable amount of experimentation is permissible, particularly if it is routine experimentation. A patent application specification is presumed to be enabled, and it is the burden of the Patent Office to present evidence to rebut this presumption. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993).

Applicants respectfully submit that evidence presented by the Examiner does not meet the burden of the Patent Office to rebut the presumption that Applicants' specification is enabled. Claim 103 is fully enabled, particularly in light of Applicants' disclosure of several examples

demonstrating how *PKHD1* sequence variants can be used diagnostically. For example, Example 4 and Tables 6-8 of Applicants' specification identify *PKHD1* sequence variants in ARPKD patients. Specifically, Example 4 teaches hybridization methods and heteroduplex analysis for screening the human PKHD1 gene for pathogenic sequence variations (listed in Table 6) and polymorphisms common in unaffected persons (Table 7). The specification at, for example, Section 7 of the Detailed Description, beginning at paragraph 0083, and Example 9 also teaches mutations that can be used for ARPKD risk assessment based on the presence or absence of pathogenic *PKHD1* sequence variants. Accordingly, a person of ordinary skill in the art would have understood upon reading the claims in light of the specification that the sequence variants codes can be used for diagnosing autosomal recessive polycystic kidney disease. The skilled artisan also would have been able to make and use the claimed method without undue experimentation.

Applicants further submit that the pre-filing date art and post-filing date art cited by the Examiner do not teach that detection according to the clamed method is unpredictable. For example, the difficulty in predicting the functional consequences and clinical manifestations of *PKHD1* sequence variants disclosed in the Bergmann et al. reference (*J. Hum. Genet.* 51:788-93 (2006); "Bergmann") is unrelated to the predictability of a diagnostic method that does not involve functional analysis. Moreover, Bergmann actually *confirms* that *PKHD1* variants are pathogenic and can be used to diagnose ARPKD. *See*, Bergmann at page 789 (second column) and page 792 (last paragraph). Similarly, the Rossetti et al. (*Kidney Intl* 64:391-403 (2003); "Rossetti") and Sharp et al. (*J. Med. Genet.* 42:336-349 (2005); "Sharp") references also confirm that pathogenic *PKHD1* variants are diagnostic of ARPKD. For example, Sharp identified several putative pathogenic sequence variants in patients diagnosed as having ARPKD. *See*, Table 1 of Sharp, which presents PKHD1 variants found in the study cohort. Sharp also describes overcoming variability in mutation detection and the frequency of missense mutations by carefully designing primers, using heteroduplex analysis, and setting forth several criteria for predicting the pathogenicity of novel sequence variants. *See*, Sharp at page 347 (section entitled "Direct gene based testing"). Finally, Sharp states that their data in combination with the teachings of Bergmann et al. could "provide an appropriate platform to beginning offering gene based diagnostic testing." Sharp at page 348 (last paragraph). Similarly, Rossetti identifies 33

PKHD1 variants and concludes that analysis of these mutations "gave a much clearer view of the type and pattern of mutations associated with ARPKD, revealed some common changes, and provided a hint of genotype/phenotype associations." *See*, Rossetti at page 400 (second column). Rossetti also states that their identification of common mutations in the ARPKD cohort is "[a]n encouraging finding from a diagnostic viewpoint." Rossetti at page 402 (first column). Thus, these post-filing date references are not evidence that *PKHD1* mutation detection is unpredictable, and rather teach the utility of *PKHD1* variants for ARPKD diagnostic purposes.

With regard to the Examiner's allegation that "extensive validation and functional analysis" of *PKHD1* sequence variants would be required for a skilled artisan to practice the presently recited method, Applicants respectfully submit that the Examiner has misunderstood the distinction between assays for detecting genetic variants and large-scale gene association studies. These research methods are distinct and yield different information about a gene of interest. Gene association studies, such as those taught in the post-filing date art cited by the Examiner, aim to discover correlations between genotype frequencies and complex diseases, typically by studying genetic and phenotypic differences between hundreds of healthy controls and diseased individuals. By contrast, diagnostic assays are based on the identification of clinically-relevant pathogenic variants. Such clinically-relevant variants can be identified and assessed for pathogenicity without significant population analysis. For example, comparative analysis using *PKHD1* orthologs and mice harboring *PKHD1* sequence variants have confirmed the pathogenicity of such sequence variants. Moreover, functional analysis of identified variants is not required since the function of polypeptides encoded by variants are irrelevant to the presently claimed diagnostic method. Therefore, the Examiner's allegation that extensive validation and functional analysis would be required to establish enablement of the presently claimed method is improper.

In light of the above, it is clear that the present claim is fully enabled. As such, Applicants respectfully request withdrawal of this rejection of claim 103 under 35 U.S.C. § 112, first paragraph.

Written Description

The Examiner rejected claim 103 under 35 U.S.C. § 112, first paragraph, alleging that it fails to comply with the written description requirement. Specifically, the Examiner alleged that the specification does not describe the claimed subject matter in such a way as to convey to one of ordinary skill in the art that Applicants were in possession of the claimed invention at the time of filing.

Applicants respectfully disagree. Written description is a question of fact, judged from the perspective of one of ordinary skill in the art. *See*, *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991). Compliance with § 112 requires sufficient information in the specification to show that the inventor possessed the invention as of the relevant filing date. *Id.* ("[T]he applicant must . . . convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention.").

For at least the reasons described above, the pre-filing date art and post-filing date art cited by the Examiner does not teach that detection according to the clamed method is unpredictable. Applicants further submit that the cited references fail to establish that Applicants' disclosure is inadequate. Applicants' specification describes several species of disease-associated sequence variants that are useful for genetic screening and diagnosing ARPKD in a subject. For example, the specification teaches using the sequence variants for detecting silent, missense, and nonsense mutations (*see*, Tables 6, 7, 10, and 12, which present single nucleotide polymorphisms in SEQ ID NO:1) for ARPKD risk assessment (*see*, e.g., the section beginning at paragraph 0083), and for mutation screening of human genomic DNA (*see*, e.g., Examples 4 and 9). Thus, Applicants respectfully submit that a person having ordinary skill in the art, reading the specification at the time of Applicants' priority date, would have recognized that Applicants were in possession of the presently claimed method.

In light of the above, it is clear that present claim 103 is adequately described. Accordingly, Applicants respectfully request withdrawal of this rejection of claim 103 under 35 U.S.C. § 112, first paragraph.

CONCLUSION

Applicants submit that claim 103 is in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Please apply any charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: September 29, 2009

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